REMARKS

Claims 1, 2, 4-7, 9-21, 25, and 27-36 are pending in the present application. Claims 6-7, 9-21, 25, 27-28, and 30-33 remain withdrawn from consideration as allegedly being drawn to non-elected subject matter. The present Communication includes no amendments and thus does not introduce any new matter. Its entry is respectfully requested. Upon entry of the present Communication, claims 1-2, 4-5, 29, and 34-36 will remain pending and under examination.

The November 18, 2008 Final Office Action

Examiner's Rejection of Claims 1 and 2 under 35 U.S.C. §102(b) Withdrawn

The Examiner's previous rejection of claims 1 and 2 under 35 U.S.C. §102(b) has been withdrawn.

In response, Applicants acknowledge and appreciate the withdrawal of the rejection.

Examiner's Rejection Under 35 U.S.C. §103

The Examiner rejected claims 1, 2, 4-7, 9-21, 25, and 27-36 under 35 USC 103(a), as allegedly obvious over the previously cited Alvira reference. According to the Examiner, "Alvira teaches the separation of R-equol from S-equol, which meets the limitation of a composition comprising R-equol." The Examiner further states that "Alvira teaches cyclodextrin (carrier) is used in separation process" and that "R-equol is the only required component for the composition claims." The Examiner acknowledges that Alvira does not teach that the combination of equol

and cyclodextrin is pharmaceutical, but states "in a claim drawn to a composition a statement to intended use (pharmaceutical) has little patentable significance." The Examiner further asserts that, "in addition, it is well known that cyclodextrin can be used in pharmaceutical compositions which makes it obvious to manufacture the combination of equol and cyclodextrin." The Examiner further asserts that Alvira teaches all that is recited in claims 4 and 5 except for the R-equol being present in 90 or 96% enantiomeric purity. In the Examiner's opinion, an artisan provided the technique of Alvira would have been able to optimize the purity of R-equol through routine experimentation even to the level of 90 or 96% purity. The Examiner further asserts that "Alvira teaches all that is recited in claim 29 except for the specified conjugates" and that "in the absence of unexpected data, it would have been obvious to employ any conjugated [sic] of the instant equol including those recited in the instant claims." The Examiner then concluded that one would have been motivated to do this "because equol and conjugates thereof would have been expected to have been equally effective."

In response, Applicants respectfully traverse the Examiner's rejection. Alvira does not teach or suggest any pharmaceutical composition; any composition "consisting essentially of" the R enantiomer of equol (R-equol) and a pharmaceutically acceptable adjuvant, carrier or excipient; any composition comprising enantiomerically pure R-equol as an active agent; or any composition formulated for oral consumption or topical application comprising R-equol wherein the composition is substantially free of S-equol. Alvira does not provide a reason or motivation to prepare such compositions, nor any suggestion that it would be desirable to do so. For at least

these reasons, therefore, and the reasons previously made of record, the rejection of the claims as obvious over Alvira, is improper and should be withdrawn.

However, in an effort to expedite allowance of the subject application, Applicants present herewith a copy of a Rule 132 Declaration by Richard L. Jackson, Ph.D., which was submitted in connection with a closely related application, U.S. Application No. 10/625,934, now U.S. Pat. No. 7,396,855. Applicants note that although the claims of the '855 patent relate primarily to the S-enantiomer of equol, and the Declaration is similarly focused, the Declaration nevertheless presents unexpected results concerning both the R- and S-enantiomers, and thus is at least as supportive of the patentability of the present claims as it is of the claims of the related issued U.S. patent. In that regard, whether the closest prior art is that referred to in the related '855 case, or the Alvira reference cited in the present case, the evidence provided in the Declaration reveals that each of the R- and S- isomers of equol exhibits properties that one of ordinary skill in the art could not have predicted.

Applicants believe the comments presented below, and the accompanying evidence of unexpected biological properties of R-equol over racemic equol (and as compared to S-equol), fully overcome the Examiner's rejections, and that the present claims are in condition for allowance.

Applicants again reiterate that the Examiner has not provided any art showing or suggesting any composition as presently claimed. Rather, the Examiner's obviousness position appears to be based at least in part on the assumption that because equol exists as a racemic

mixture and thus could presumably be separated into its R- and S- enantiomers, one of ordinary skill in the art would have been motivated to obtain these individual equol enantiomers for use in compositions such as those claimed herein.

Applicants also note that relevant caselaw reflects the common presumption that biological activity typically resides in one enantiomer obtained from a racemate. More particularly, the presumption is that the activity of one enantiomer will be twice that of the racemate, owing to the belief that the other enantiomer is inactive. Under this rationale, one of ordinary skill in the art would have been led to expect that if a racemic equol mixture is active, the activity can be attributed to the fact that one of the enantiomers, i.e., either the S-, or the R-, is solely responsible for the activity. A showing of unexpected properties of enantiomeric equol over the cited art's teachings of racemic equol therefore would be sufficient to overcome the obviousness rejection.

Accordingly, Applicants now provide (via the attached copy of the Declaration submitted in the related application) data showing various surprising results, including unexpected properties possessed by the equol enantiomers, that are not possessed by the racemic mixture. The results, which are discussed herein support the Applicants' position that the present claims are not obvious over the art cited by the Examiner.

In that regard, the data presented includes a collection of biochemical assays in which the biological activities of R-equol, S-equol, and racemic equol were evaluated and the results directly compared with each other. Specifically, each of R-equol, S-equol, and racemic equol

was screened against a broad spectrum of receptor systems using standard radioligand binding assay methods adapted from the scientific literature. Reference standards were run as an integral part of each assay to ensure the validity of the results obtained. Percent inhibition results of the complete, broad spectrum of assays are reported, with the most pertinent results discussed herein.

The data clearly reflect results that are contrary to the accepted wisdom noted above, namely, that in any given system, one of the enantiomers would be active, the other inactive, and the racemate having activity residing approximately halfway between the two. This model clearly has been shown not to be universal among the systems tested. In fact, some receptor systems yielded effects that do not fit within any model of predictability. Indeed, as the data show, in some systems, the S-enantiomer is active while the R- is not. In others, the R-enantiomer is active while the S- is not. In some systems, all three are active, and in one particular system, discussed more fully below and in the attached Declaration, both the S- and R-enantiomers are similarly active, but the racemate is inactive. It is also seen that there is even variability in activity between related receptor types.

Overall, the unusual variability in these data is, in itself, unexpected and indicative that the simple, conventional wisdom concerning the behavior of racemic mixtures in comparison to the individual enantiomers, or the individual enantiomers in relation to each other, does not apply with respect to equol. These data show that it simply would not have been obvious to prepare a successful enantiomeric or non-racemic equol composition as claimed herein, merely on the basis that racemic equol and therefore its individual enantiomers, were known to exist and might have

some usefulness.

The table below summarizes some of the more significant individual results obtained in the broad spectrum of studies, which support further the non-obviousness of enantiomeric equol compositions.

In vitro Pharmacological Screening

Target	**Percent Inhibition (at 10 uM)**			**Interpretation (re: higher values)**
	S-Equol	**R-Equol**	**Racemate**	
ERα	92	93	94	Positive control
ERβ	98	94	98	Positive control
src Protein Tyrosine Kinase LCK	27	26	1	Oncology indication
Transcription Response Factor, NF-AT	5	32	19	Anti-inflammatory indication, potential MOA
G Protein-coupled Receptor 103	58	14	38	Bone sparing, satiety, CNS effects, inflammation
Monoamine Transporter	16	51	49	CNS, antidepressant
NE Transporter	57	37	50	Antidepressant
Dopamine Transporter	84	88	92	Anti-Parkinsonism

As is evident from the above, the typical approach of simply resolving a racemate into its separate enantiomers, determining which of the two isomers is the active form (and which is the inactive form), and consequently choosing to prepare a composition using that active form, would not be appropriate with respect to equol. One cannot reliably predict anything with

respect to biological activity of the equol enantiomers, when armed only with the prior art teachings concerning the racemic mixture.

The src Protein Tyrosine Kinase (LCK) data, for example, provides a particularly interesting, and undoubtedly unexpected result. LCK is an important receptor kinase that regulates the growth of cells. When mutated, uncontrolled growth occurs. The studies here have shown that both S- and R-equol inhibit this activity approximately equally. However, racemic equol, which of course contains both R- and S-equol, surprisingly does not inhibit the activity. This is a completely unexpected finding. One simply could not have expected activity in either enantiomer, when the racemic mixture containing the two enantiomers is *inactive*. Based on these results, therefore, racemic equol would be ineffective, for example, in inhibiting cancer growth, but a composition as claimed herein, containing enantiomeric equol (the R-enantiomer in this case), would surprisingly show potential benefits. This is clear evidence of at least one unexpected property possessed by the R-enantiomer that is not possessed by the racemic mixture. In that regard, Applicants respectfully direct Examiner's attention to MPEP §716.02(a)(III), which recites that "[p]resence of a property not possessed by the prior art is evidence of nonobviousness." While this particular unexpected and surprising result is, in itself, sufficient in Applicants' view to support the present claims' nonobvious over the art's teachings with respect to racemic equol, nonobviousness of the claimed invention is also strongly supported by the totality of the evidence provided herein.

Applicants have presented evidence, therefore, that non-racemic equol compositions, including R-equol compositions, possess unexpected properties at least not possessed by the racemic mixture. Accordingly, Applicants believe the Examiner's obviousness rejection has been fully overcome. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection set forth under 35 U.S.C. §103.

Examiner's Double Patenting Rejection

The Examiner maintained the previous provisional obviousness-type double patenting rejection of claims 1 and 2 over U.S. Application No. 10/625,934 (which is the now issued '855 patent noted throughout this paper). The Examiner indicated that the rejection will be held in abeyance until the indication of allowable subject matter in the present application. In response, Applicants appreciate the Examiner's willingness to do so.

Concurrently filed Information Disclosure Statement

Applicants are concurrently filing an Information Disclosure Statement (IDS), which includes copies of papers filed in pending U.S. Application No. 11/059,951. Applicants have become aware of these papers through the USPTO's public PAIR database. Similar papers have also been filed in a case related to the '951 application, namely U.S. Application No. 10/533,045. Both of these applications have an inventor (Kenneth Setchell) and an assignee (Children's Hospital Medical Center) in common with the present application, but are not otherwise related

to the present application, and are not being prosecuted by the undersigned attorney. Moreover, both have already been made of record in the present application by their inclusion in an earlier filed IDS.

The information being submitted in the concurrently filed IDS includes an Amendment and Declaration submitted in response to rejections made in the '951 application, which rejections cited WO 2004/009035, international counterpart to the present application. In the response, in an attempt to dispose of the prior art effect of the cited international application, arguments were advanced asserting that certain subject matter disclosed in the reference (and thus, by implication, the current application) was invented by the Declarant and the other named inventors of the '951 application. Notwithstanding these assertions, Applicants understand the inventorship of the present application to be correct and do not believe the information presented in the '951 and '045 applications affects the patentability of any of the pending claims of the present application. Thus, the submission of the IDS should not be construed as an admission to the contrary.

In view of the above remarks and evidence, Applicants believe all of the Examiner's concerns set forth in the November 18, 2008 Final Office Action have been fully overcome and that the claims are in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

April 20, 2009 By _____

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Attachment: Copy of Rule 132 Declaration previously submitted in related application

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